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Acute risk factors in fatal opioid overdoses as a result of hypoxia and cardiotoxicity. A systematic review and critical appraisal

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Summary

Background: The rates of fatal opioid overdoses (FOO) have increased rapidly over the last 10 years. The actual phenomenon occurs as a result of a toxic opioid effect on the cardiorespiratory system. **Aims:** The systematic review aimed to identify the acute risk factors in fatal opioid overdose (FOO) as a result of hypoxia and cardiotoxicity. **Methods:** A systematic review was undertaken. The selection of papers has utilised rigorous criteria of inclusion/exclusion, controlled for heterogeneity. **Results:** A total of thirteen articles met the inclusion criteria. Ten of the thirteen studies included were retrospective and the other three studies employed different designs namely longitudinal cohort, case control and case cohort. Factors that were modestly described with increased acute risk of FOO due to hypoxia and cardiotoxicity include multiple sedative use (opioids and alcohol), reduced tolerance and presence of an acute painful condition. **Conclusion:** This systematic review has highlighted the lack of information on acute risk factors of FOO due to hypoxia and cardiotoxicity. Future studies need to explore possible mechanisms underlying cardiotoxicity such as reported changes in arterial stiffness in opioid dependent populations and the unexplored potential effects on endothelial function.

Key Words: Fatal opioid overdose; hypoxia, cardiotoxicity, acute risk factor

1. Introduction

Rates of fatal opioid overdoses (FOO) have increased rapidly over the last 30 years [25]. For example, in 2010, the average EU mortality rate was estimated at 13 overdose deaths per million in population, with higher rates among younger cohorts. Among the adult population the estimated rate of FOO is 18.3 deaths per million. The use of opioids, in particular the use of heroin, accounts for 74% of overdose deaths in Europe [49].

Both acute and chronic risk factors [54, 38] identified in the literature were grouped into the following domains of (1) polydrug use and other drug taking behaviours, (2) comorbid health issues and (3) prescribing. Overall, those who overdose tend to be males with a long history of substance abuse, co-morbid depressive disorders [3] have a propensity to engage in polydrug use [9, 32], require assistance with injection, and have a history of being denied or non-complying to treatment [49,13,55,10]. In the UK and other European countries, most illicit substance-related fatal overdoses involve opioids [16, 15, 14, 21]. The concurrent use of heroin combined with alcohol and benzodiazepines poses a particular threat, as the presence of such central nervous system depressants can cause a drug user's normal heroin dosage to prove fatal [41]. An individual's tolerance to a particular substance can also be reduced during a period of forced abstinence such as during incarceration [29]

However, despite having gained knowledge of

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these mainly chronic factors FOO continues to be a significant contributor to the mortality of dependent individuals [13].

The primary mechanism of death is opioid-induced respiratory depression, although hypoxia-induced cardiac arrest and arrhythmia may also occur [19, 24, 51]. In such cases of FOO, the victim's breathing slows to the point where oxygen levels in the blood fall below the level needed to transfer oxygen to the vital organs. As oxygen saturation (normally greater than 97 per cent) falls below 86 per cent, the brain struggles to function. Typically, the individual becomes unresponsive, blood pressure progressively decreases and the heart rate slows, ultimately leading to cardiac arrest. Death can occur within minutes of opioid ingestion but often, prior to death there is a longer period of unresponsiveness lasting up to several hours. This period is sometimes associated with loud snoring, leading to the term 'unrousable snorers' [52].

There is a fundamental limitation to the interpretations of acute factors. Methodologically the information collated is based on a flawed assumption that all FOO cases have had a: (1) comprehensive and timely police identification and (2) comprehensive toxicological analysis to all licit and illicit substances and (3) an objective contextualised and evidence based interpretation of the data obtained from both toxicology and post-mortem results [19]. This is compounded by the fact that the definition of an FOO is not only complex, but with individual studies adopting specific definitions, which vary depending upon the focus of the study and also upon the competencies of the individuals determining if such a case is an FOO or not [26]. Therefore such interpretations are currently due to the interpretation of the toxicology results rather than to a standardised, objective, reproducible and valid operationalised process to identifying FOO [23].

The aim of this systematic review was to focus on the acute risk factors contributing to fatal opioid overdose as a result of hypoxia and/or cardiotoxicity.

2. Methods

Systematic reviews providing a logical, transparent and reproducible synthesis of all current literature evidence, within specified criteria, seem an ideal framework to study healthcare issues [7] such as acute risk factors contributing to FOO as a result of hypoxia and/or cardiotoxicity. This systematic review was based upon the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [43].

2.1. Search strategy

The following electronic databases were searched: PUBMED (1950 to 2013), PsycINFO (1940 to 2013), CINAHL (1940 to 2013). In order to select the maximum number of relevant references a search strategy consisting of the following terms were applied when available: Risk factors/hypoxia/cardiotoxicity/sociocultural factors/psychosocial factors/risk assessment AND opioids/analgesics, narcotics/opiate alkaloids/opium/morphine/methadone/buprenorphine/heroin OR opioids/analgesics/narcotics/opiate alkaloids/opium/morphine/methadone/buprenorphine/heroin AND fatal outcome/mortality/death/hypoxia/cardiotoxocity/poisoning/overdose/fatal.

2.2. Included studies

Studies included in the review were required to deal with all of the following elements:

Opioids: The term encompasses opiates (naturally obtained alkaloids from the resin of the opium poppy) as well as synthetic opioids [31]. Articles which examined a broader spectrum of drugs were included provided results were available which referred to opioids specifically.

Fatal overdose: Opioid overdose deaths are those caused by acute respiratory depression as a direct consequence of the drug administration (i.e. hypoxia) [51]. This review was interested in determining the risk factors for fatal overdoses as opposed to non-fatal. Given this, articles which looked at overdoses in general were included only when results for fatal and non-fatal were provided independently. Those articles concerned with deaths related to the chronic effects of drug use, such as systemic diseases for example liver pathology or road traffic accidents, were not included in this review. Articles which looked at overall mortality from drug use were included provided results were available which referred to opioid overdose specifically.

Risk factors: For the purposes of this review these were defined as any characteristic, condition, or behaviour associated with an increased risk of hypoxia and/or cardiotoxicity resulting in FOO. Predisposing factors (genetic, attitudinal, personality, and environmental factors associated with health, or lack of it) in a person [31] were not included in this review. This review focused on deaths clearly attributed to an

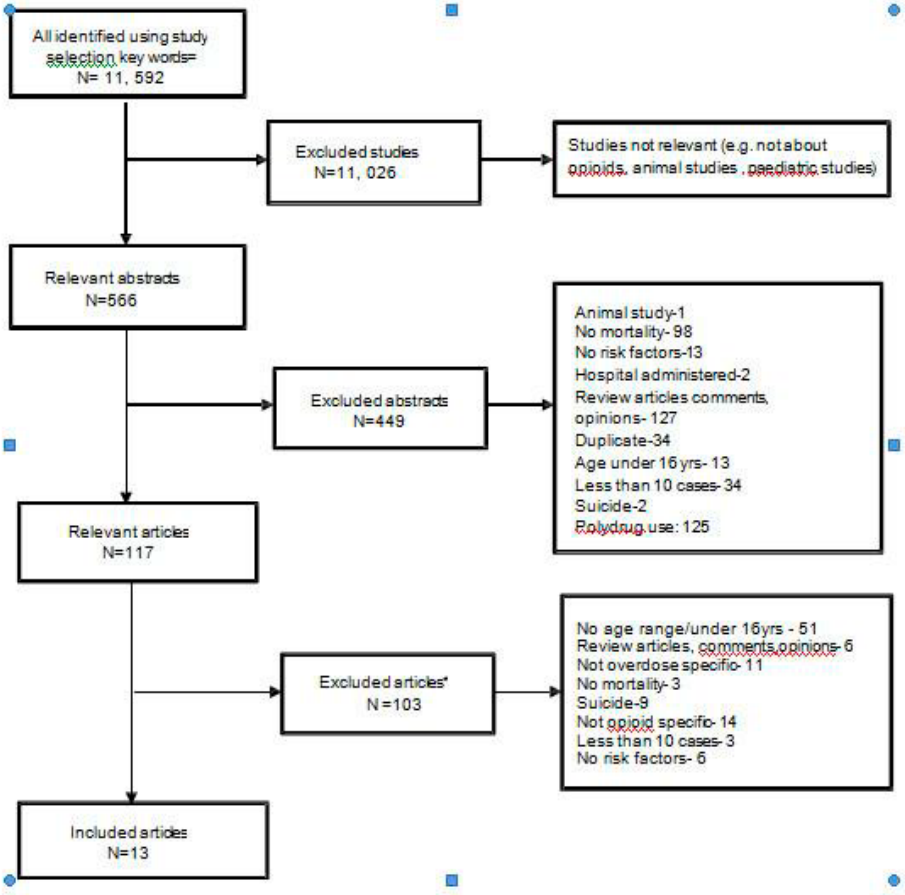

Figure 1. Identified studies

episode of hypoxia and/or cardiotoxicity.

Age range: Drug metabolism is different in adults than in children [8], hence, it was prudent to consider risk factors for childhood and adult overdoses separately. Participants in studies met a minimum age requirement of 16 years in order to be included. Studies which provided a mean age of participant, but no age range, were therefore excluded.

Self-administered: The opioids were required to be self-administered for inclusion in the review. With the exclusion of reports referring to hospital administered opioids, this review avoided the complex administrative errors within the healthcare system which unfortunately are known to cause opioid overdoses [48].

Accidental: This study was concerned specifically with accidental (non-deliberate) overdose deaths and not suicides from opioid overdose. Risk factors for suicides are likely to be different from accidental overdose (e.g. may involve more psychiatric co-morbidities) [17].

Number of overdose deaths: It is difficult to ascertain the relevance of any given finding from studies involving very few subjects and therefore only larger studies were included. The criteria of, at least 10 opioid deaths, was applied to satisfy this specification.

2.3. *Study design, selection process and data extraction*

All types of experimental designs were included in this systematic review [36]. Data were extracted by two reviewers using a 'search diary' created listing the names of the databases searched, the keywords used and the search results.

The initial selection process involved reading the titles of the search results and discarding those which were obviously irrelevant to this review. Those titles in which there was ambiguity regarding their relevance were still included. This approach left less risk of excluding relevant articles at this early stage. Fol-

Table 1- General characteristics of selected studies

Study	Mean Age (years)	Male (%)	Ethnicity (%)	Country	Type of opioid	Opioid deaths examined (N)	Study type
Green *et al.* (2011)	n/a	70.5	Caucasian-93 Other-7	USA	Opioid	1975	Retrospective cohort
Minett *et al.* (2010)	38.8	72	n/a	USA	Opiates	161	Retrospective cohort
Henderson *et al.* (1991)	32.5	78	Caucasian-50 Hispanic-29 Black-20 Asian-1	USA	Fentanyl	112	Retrospective cohort
Darke *et al.* (1999)	29.2	87	n/a	Australia	Heroin	61	Retrospective cohort
Perret *et al.* (2000)	n/a	85	n/a	Switzerland	Methadone/ morphine	36	Retrospective cohort
Fugelstad *et al.* (2003)	n/a	87	n/a	Sweden	Heroin	192	Retrospective cohort
Wolf *et al.* (2004)	38.6	78.4	Caucasian- 96 Black-4	USA	Methadone	98	Retrospective cohort
Thiblin *et al.* (2004)	n/a	85	n/a	Sweden	Heroin	192	Retrospective cohort
Ødegart *et al.* (2007)	32.9	65	n/a	Norway	Opioid	88	Longitudinal Cohort
Oliver *et al.* (2007)	32	94	Caucasian	UK	Opiates	15	Case-control
Bohnert *et al.* (2011)	n/a	93	Black – 6.9 White- 83.6 Hispanic- 3.1 Other- 9.7	USA	Opioid	750	Case Cohort
Darke *et al.* (1997)	28	70	n/a	Australia	Heroin	39	Retrospective cohort
Tagliaro *et al.* (1998)	n/a	78.4	n/a	Italy	Heroin	37	Retrospective cohort

N= number; n/a= not available; opioids=any drug which produce their effects through activity at the mu, kappa and delta receptors; opiates= opioids naturally obtained from the resin of the opium poppy; morphine= a specific alkaloid extracted from opium; heroin= a powder derived from morphine; methadone=a synthetic opioid C 21 H
27 NO used in heroin addiction treatment and analgesia; fentanyl= a synthetic opioid $C_{22}H_{28}N_2O$ used in analgesia (definitions from Merriam-Webster Medical Dictionary; available at http://www.merriam-webster.com/)

lowing this, these abstracts and those found through snowballing techniques were reviewed and matched to the inclusion criteria. Those articles which met the criteria and those in which it was unclear were then read in full. Finally, only those in which the full article matched the inclusion criteria were included in the review. The acute risk factors identified from these papers were then arbitrarily recorded and listed into the following areas: (1) drug taking behaviours and purity, and (2) prescribing and treatment.

2.4. Data analysis

There was no attempt to undertake any meta-analyses, exploring associations or correlations, and our approach was just systematically descriptive.

3. Results

3.1. Included articles

A total of thirteen articles were found in which acute risk factors for FOO were quantified [5, 11, 10, 18, 20, 22, 30, 33, 34, 35, 44, 46, 53, 4] (Figure 1).

The total number of potential FOO incidents investigated was 3803. The mean age of overdose victims was 33.1 years and about 80% were male. Ten of the thirteen included articles were retrospective studies in which post-mortem autopsy and toxicology examinations were performed. The remaining three studies employed different designs namely longitudinal cohort, case control and case cohort. The oldest article included was dated 1991 (Table 1).

Table 2: Presence of plasma levels in FOO cases

STUDY	Total Number (N)	Alcohol % (n)	Benzo	Antidepressants	Cocaine	Amphetamine	Cannabis	Combined Alcohol and BZ	Combined BZ and Cocaine
Green et al. 2011	1975	21(419)	10 (201)	2(41)	28(551)	n/a	n/a	n/a	n/a
Minett *et al.* 2010	161	31(50)	22(35)	18(29)	44(7)	n/a	12(19)	n/a	n/a
Thiblin *et al.* 2004	192	46(109)	48(114)	n/a	n/a	n/a	17(39)	n/a	n/a
Wolf *et al.* 2004	98	9(9)	24(23)	n/a	21(20)	n/a	5(5)	n/a	25(24)
Fugelstad *et al.* 2003	192	29(55)	40(76)	n/a	0.5(1)	7(13)	20(39)	17(33)	n/a
Perret *et a*l. 2000	36	30(11)	50(18)	n/a	17(6)	n/a	n/a	n/a	n/a
Darke *et al.* 1999	61	33(20)	33(20)	n/a	n/a	n/a	n/a	7(4)	n/a
Darke *et al.* 1997	39	51(20)	21(8)	n/a	n/a	n/a	n/a	10(4)	n/a
Henderson *et al.* 1991	112	38(34)	7(8)	1(2)	16(18)	5(5)	n/a	n/a	n/a
MEAN		32%	28%	3%	5%	2%	2%	11%	

n/a = not available

3.2. Excluded studies

Fifty one from the 103 articles excluded after a full reading did not provide an age range and/or the age of subjects accepted was younger than 16 years. Fourteen articles were excluded because, although they discussed overdose mortalities, they did not deal with risk factors for opioids specifically. Eleven articles looked at mortality, often drug related, but did not specify that the mortality was caused by an opioid overdose. Other reasons for exclusion were papers describing less than ten mortalities (N=3), not discussing mortality at all (N=3), not discussing relevant risk factors (N=6), including suicides (N=9) and/or

Table 3: Concentration of opioid levels in relation to alcohol and benzodiazepine concentration levels

Study	Alcohol concentration levels
Minett *et al.* (2010)	There was no significant difference in morphine concentrations identified in samples with detectable post-mortem concentrations of alcohol equal to or less than the median value of ethanol versus those greater than the median ($p<0.5$)
Darke *et al.* (1999)	Morphine concentrations among cases involving alcohol ranged well below the toxic level for opioid naïve individuals.
Fugelstad *et al.* (2003)	A high blood ethanol level was significantly associated with low morphine and 6-MAM levels ($p<0.01$)
Darke *et al.* (1997)	There was a significant negative correlation between blood alcohol and blood morphine concentrations among fatal cases ($p<0.001$; $r^2=-0.41$)
Study	Benzodiazepine concentration levels
Minett *et al.* (2010)	There was no significant difference in morphine concentrations in samples with detectable post-mortem concentrations of benzodiazepines equal to or less than the median value versus those greater than the median ($p<0.2$)
Fugelstad *et al.* (2003)	Higher levels of 6-MAM were associated with the presence of benzodiazepines ($p=0.01$).
Wolf *et al.* (2004)	The mean methadone concentration among cases with co-intoxication with benzodiazepines was 0.43 mg/L. The mean methadone concentration among cases with deaths attributed to methadone toxicity alone was 0.56 mg/L.

p=probability

being review articles (N=6).

3.3. Acute risk factors

3.3.1. Drug taking behaviours and purity

3.3.1.1. Polydrug use

3.3.1.1.1. Alcool

Nine of thirteen studies measured the percentage of overdose victims with a positive blood alcohol level (Table 2). The lowest percentage of cases in which alcohol was detected was 9% [53] and the highest was 51% [10]. However, the presence of alcohol in fatal overdose victims could be an incidental finding. Based on the assumption that the presence of alcohol is a risk factor, lower concentrations of opioid levels may be fatal due to the summative sedative effects of alcohol and opioids taken together. Four studies measured concentration of opioid levels in relation to alcohol concentration in order to investigate what role alcohol may have played in the deaths [10, 11, 18, 30] (Table 3).

The role of alcohol may not be as straightforward as alcohol levels being proportional to an increased risk of death. Fugelstad et al. indicated that blood ethanol levels exceeding 0.5 mg/g were needed for an increased risk and that this significance on dose declined at higher levels of ethanol [18]. Thiblin et al. noted that complete long term abstinence from alcohol was, in fact, found to be a significant (10% contribution) risk factor [46]. The association was thought to be due to the significantly higher proportion of alcohol abstainers who report daily use of heroin the year before hospital admission than among those who report use of alcohol (75% vs 53%, $p< 0.001$). Therefore, it appears alcohol concentrations above a certain level do increase acute risk of FOO. However, those who completely abstain from alcohol may be at an increased risk of FOO, not as a result of their lack of alcohol use, but as they are more likely to be using heroin on a regular basis.

3.3.1.1.2.Benzodiazepines

Nine of the thirteen studies measured the percentage of FOO victims that were positive for benzodiazepines [10,11,18,20,22,35,46,53]. The lowest percentage of cases found was 7% [22] and the highest was 50% [35]. Three studies looked at the acute effect of benzodiazepines on fatal opioid concentrations [18,30,53] (Table 3) but the findings were inconclusive.

3.3.1.1.3.Other drugs and combination of drugs

Aside from alcohol and benzodiazepines, other drugs were found to be contributory acute risk factors in FOO in seven studies [18, 20, 22, 30, 35, 46, 53]. These other drugs identified in victims were cocaine, anti-depressants, amphetamine and cannabis. Only two studies examined effects of these on opioid levels [18,30]. Minett et al. [30] found that "morphine concentrations were higher in the ''high'' concentration group of the antidepressant drug class subset and lower in the ''low'' concentration group ($p=0.03$)''. Fugelstad et al. [18] found that presence of THC (a cannabis metabolite) was associated with significantly ($p=0.02$) lower levels of 6-MAM (a morphine metabolite), suggesting that cannabis could increase risk of FOO. Combination of opioids with both benzodiazepines and alcohol was considered as the most common lethal drug cocktail [10,11,18].

3.3.1.2. Route of administration

Only one study [46] examined the role of route of administration in overdose fatalities. It found that injection and non-injection routes of administration can be equally lethal. In fatal overdose episodes where the route of administration was not injection, median morphine concentrations were significantly ($p=0.002$) lower than in those who overdosed by injection.

3.3.1.3. Opioid use after abstinence

Five studies discussed the role of reduced opioid tolerance after a period of abstinence in FOO [18, 22, 34, 44, 46]. All of these studies noted that the majority of overdose victims in their studies had occurred

Table 4: Mean morphine concentration in hair samples [44]

Subjects	Mean (ng/mg)	SD	Range (ng/mg)
Fatal Overdose	1·2	2·4	0–12·2
Active Heroin Addicts	6·1	4·3	1·2–17
Abstinent Former Addicts	0·7	0·9	0·1–3·3

SD= Standard Deviation

in individuals with reduced tolerance as a result of a period of abstinence and/or diminished drug use but gave no further information.

A single study focused on abstinence as an acute risk factor [44] and found that FOO victims had significantly ($p<0.001$) lower levels of morphine in hair samples than active heroin users. However, their morphine levels were not significantly ($p=0.98$) different from former addicts who had been abstaining for several months previous to the study. They concluded that most of the FOO victims had been abstaining in the months previous to their death (Table 4).

Imprisonment is a common cause of abstinence among opioid users and release from prison has been associated with an increased risk of overdose [4]. In this review, just three studies stated rates of recent prison release amongst victims of FOO. No further information was given regarding how this related to opioid levels.

3.3.1.4. Purity of illicit opioids

Three studies commented on the effects of purity on risk of FOO [31,34,35]. Green et al. [20] and Henderson et al. [22] both found that the peak rate of FOO coincided with the peak purity levels of the drugs. However it is also worth noting that in both cases this coincided with lowest heroin prices and highest availability which could have meant increased use was responsible for any increase in FOO. Indeed, Henderson et al. concluded that 'the incidence of fentanyl-related deaths is probably determined by the general availability of the drug, rather than the relative potency of the analogues'.

Darke et al. [11] measured the range and mean heroin purity per fortnight from a total of 322 heroin samples analysed over a 2 year period when a total of 61 FOO episodes occurred in the region. The study found that both the range and mean heroin purity 'were independent predictors of the number of fatalities per fortnight'. Their findings were statistically significant ($p<0.001$) and accounted for 40% of the variance, suggesting that purity plays a major role in FOO.

3.3.2. Prescribing

Just one study included in this review covered the topic of prescribed opioids for analgesic purposes. Using a cohort study design, Bohnert et al. [5] found that in comparison with other individuals prescribed opioid medication, those who had suffered a FOO were significantly more likely to have an acute pain condition ($p<0.001$). Further to this, the article described those at greatest risk were prescribed a daily scheduled opioid in addition to a required opioid. The daily scheduled dose was also found to be an important factor in those with acute pain conditions with acute risk of FOO increasing significantly ($p <0.05$) with size of dose, particularly those doses above 50mg daily. The results of this study strongly suggest acute pain may be a significant risk factor for FOO from hypoxia and/or cardiotoxicity.

4. Discussion

This review has analysed different acute risk factors for FOO as a result of hypoxia and/or cardiotoxicity. The innovative aspect of this review is that it is focused on specific acute risk factors and utilised better criteria of inclusion/exclusion.

4.1. Main findings

The most robust acute risk factor identified was concomitant alcohol use and negative correlations with blood opioid levels. This finding is in agreement with a number of studies, whose evidence is relevant though they did not meet the inclusion criteria for this review [56,39,40]. Alcohol is a depressant which works via the GABA receptors to produce inhibition which affects the respiratory centres [2]. When these inhibitory effects are combined with the inhibitory effects of opioids from their action on μ receptors, it is thought to lead to further depression at the respiratory centres [51]. Benzodiazepines produce their effects through a similar mechanism to alcohol, involving GABA receptor binding but binds at an alternative site [51]. Although they were a commonly detected drug group in victims (mean 28%), this review found their role in FOO to be less straightforward than that of alcohol alone with very mixed results seen across a small number of studies.

In addition to alcohol, the loss of tolerance to opioids due to abstaining from opioids and high purity of opioids taken before deaths emerged as other acute risk factors [44]. Acute pain conditions and concomitant daily use of strong prescribed opioids (e,g, morphine and oxycodone) were also associated with FOO. Other studies have also found higher daily doses to be associated with greater risk of overdose [12].

Limitations

There are a number of limitations to this review.

Some are related to the methods used in systematic reviews. For example this review may suffer publication bias potentially leading to over-representation of significant or positive studies in systematic reviews [43]. Strict inclusion criteria were applied and this limited the number of acute risk factors identified. This may have resulted in an incomplete assessment of potential risk factors. Additionally an arbitrary figure of 10 cases was chosen to be the minimum number of overdoses for studies to be included in the review. In Wolf et al. [53], 29% of the cohort studied represented individuals using methadone for pain relief whereas the study by Darke et al. [11] involved individuals who had overdosed on illicit heroin. The heterogenous demographics of such populations may be contributory to the differences observed in the inconsistent frequency of alcohol detected in these two groups. Additionally, there was a nine year difference when Henderson et al. (1991) and Perret et al. (2000) studies were conducted in the USA [22] and Europe [35], respectively. Given this, the findings on benzodiazepine use could reflect cross cultural differences in use across different decades as there is evidence that use of benzodiazepines by young people increased during this time [28].

Others are specific to this review. Most studies had small sample sizes. There was an over representation of articles looking at specific acute risk factors, whereas others had fewer studies investigating them. This led to further difficulties in interpreting the impact of their findings [50]. Furthermore, most of the studies in this review provided information from toxicology findings during post-mortem examination, giving a very narrow perspective of the factors involved which might have contributed to the hypoxic and/or cardiotoxic event.

Future directions

This systematic review has highlighted the lack of information on other acute risk factors that might be associated with precipitating an FOO. Future studies need to explore possible mechanisms underlying cardiotoxicity such as reported changes in arterial stiffness in opioid dependent populations [6,37] and the unexplored potential effects on endothelial function [27]. Opioid induced hypoxia and cardiotoxicity is usually regarded as a consequence of an overdose syndrome. However infrared spectroscopy and other similar methods show significant acute decreases in cortical haemoglobin oxygenation in opioid dependent individuals [42]. The result of this review did not undertake to explain the potential influence/s on FOO of premorbid reduction in oxygen saturation during sleep [47], blunted hypercapnic ventilatory response (HCVR) and hypoxic ventilatory responses (HVR) in opioid dependent individuals [45]. This is compounded by the known cardiotoxic effects of opioids [6] and associated ischaemic changes in the opioid using population [1]. Future studies should investigate these potential biological and mechanistic factors that might lead to susceptible individuals having a fatal opioid overdose.

5. Conclusions

The limited number of studies identified in this review highlights the need to investigate further with detailed biological markers the conditions why some individuals die of an opioid related hypoxic or cardiotoxic event, but also the premorbid conditions that might make some individuals more susceptible to a fatal hypoxic/cardiotoxic outcome. This will support further the notion that fatal overdoses are a combination of acute and premorbid risk factors that might have a biological and mechanistic basis.

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Contributors

AB conceived the study, participated in its design, carried out the systematic review and co-ordinated and helped with the manuscript. ST carried out the systematic review, participated in the analysis and drafting of the manuscript. FK, GH and GC participated in the design of the study and helped with the manuscript. All authors read and approved the final manuscript.

Conflict of interest

None

Ethics

The work done for this paper does not involve humans in any way and therefore does not require IRB or other ethics committee approval and informed consent.

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